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| APPLICATION NO. | FILING DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO. | CONFIRMATION NO. |
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| 10/645,930 | 08/22/2003 | Carsten Buhmann | A9276 | 8279 |

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DAVID W. HIGHET
BECTON, DICKINSON AND COMPANY
1 BECTON DRIVE, MC110
FRANKLIN LAKES, NJ 07417

| EXAMINER | |
|---|---|
| WANG, CHANG YU | |
| **ART UNIT** | **PAPER NUMBER** |
| 1649 | |

| SHORTENED STATUTORY PERIOD OF RESPONSE | MAIL DATE | DELIVERY MODE |
|---|---|---|
| 3 MONTHS | 02/27/2007 | PAPER |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/645,930 | BUHMANN ET AL. | |
| | Examiner | Art Unit | |
| | Chang-Yu Wang | 1649 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *30 November 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *2,3,11,12 and 18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-10 and 13-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *22 August 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *1/27/05,1/8/04,12/01/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Status of Application Election/Restrictions*

Applicant's election without traverse of Group III in the reply filed on Nov 30, 2006 is acknowledged.

Claims 1-18 are pending. Claims 2, 3, 11, 12 and 18 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to nonelected inventions, there being no allowable generic or linking claim. Claims 1, 4-10 and 13-17 are under examination in this office action.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 8, 9 and 17 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. In addition, were the deposit requirements met, claims 8, 9 and 17 would still be rejected as lacking enablement commensurate in scope with the claims for the reasons set forth in the rejection below. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The invention appears to employ novel biological materials, specifically NCAM 14.2 antibody and neuro 4.1 antibody. Since the biological materials are essential to

the claimed invention they must be obtainable by a repeatable method set forth in the specification or otherwise readily available to the public. If the biological materials are not so obtainable or available, the requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the biological materials. The specification does not disclose a repeatable process to obtain the biological materials since the antibodies are derived from a hybridoma screening and it is not apparent if the biological materials are readily available to the public. It is noted that Applicant has described a method of making the monoclonal antibodies (p. 22 of the specification), but there is no indication in the specification as to public availability. If the deposit is made under the Budapest Treaty, then an affidavit or declaration by Applicant, or a statement by an attorney of record over his or her signature and registration number, stating that the specific biological materials have been deposited under the Budapest Treaty and that the biological materials will be irrevocably and without restriction or condition released to the public upon the issuance of a patent, would satisfy the deposit requirement made herein. If the deposit has not been made under the Budapest Treaty, then in order to certify that the deposit meets the criteria set forth in 37 C.F.R. §§ 1.801-1.809, Applicant may provide assurance of compliance by an affidavit or declaration, or by a statement by an attorney of record over his or her signature and registration number, showing that:

(a) during the pendency of this application, access to the invention will be afforded to the Commissioner upon request;

(b) all restrictions upon availability to the public will be irrevocably removed upon granting of the patent;

(c) the deposit will be maintained in a public depository for a period of 30 years or 5 years after the last request or for the effective life of the patent, whichever is longer;

(d) a test of the viability of the biological material at the time of deposit will be made (see 37 C.F.R. § 1.807); and

(e) the deposit will be replaced if it should ever become inviable.

Applicant's attention is directed to M.P.E.P. §2400 in general, and specifically to §2411.05, as well as to 37 C.F.R. § 1.809(d), wherein it is set forth that "the specification shall contain the accession number for the deposit, the date of the deposit, the name and address of the depository, and a description of the deposited material sufficient to specifically identify it and to permit examination." The specification should be amended to include this information, however, Applicant is cautioned to avoid the entry of new matter into the specification by adding any other information. Finally, Applicant is advised that the address for the ATCC has changed, and that the new address should appear in the specification. The new address is:

American Type Culture Collection

10801 University Boulevard

Manassas, VA 20110-2209

Claims 1, 4-10, 13-17 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for detecting higher levels of NCAM and L1 in the CSF from patients with Alzheimer's disease, vascular dementia, dementia of mixed type by ELISA with anti-NCAM and anti-L1 antibodies, does not reasonably provide enablement for a method for diagnosing all dementia-related neurological

disorders by detecting a higher level of L1 or NCAM in all types of samples of patients as broadly claimed. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

"There are many factors to be considered when determining whether there is sufficient evidence to support a determination that a disclosure does not satisfy the enablement requirement and whether any necessary experimentation is 'undue'. These factors include, but are not limited to:

(A) The breadth of the claims;

(B) The nature of the invention;

(C) The state of the prior art;

(D) The level of one of ordinary skill;

(E) The level of predictability in the art;

(F) The amount of direction provided by the inventor;

(G) The existence of working examples; and

(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

*In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)". See MPEP § 2164.01.

Claims 1, 4-10, 13-17 are directed to a method of diagnosing a dementia-related neurological disorder in a patient with symptoms of dementia-related neurological disorders or suspected of having the dementia-related neurological disorders. The

method comprises obtaining a sample from a patient and detecting a higher level of L1 or NCAM in the patient, which would be a diagnostic marker of a dementia-related neurological disease. Applicant shows that the levels of NCAM and L1 are increased in the CSF from patients with Alzheimer's disease, vascular dementia (VD) and dementia of mixed type (MT) but not other diseases. The levels of L1 do not show any difference in multiple system atrophy, Parkinson disease, diffuse Lewy body dementia, epilepsy, amyotrophic lateral sclerosis, polyneuropathy, or multiple sclerosis as compared to the normal controls. The levels of NCAM are decreased in the CSF from patients with multiple sclerosis. Applicant further analyzed whether the levels of NCAM and L1 are associated with dementia that was diagnosed based on the Mini Mental State Examine (MMSE) and whether the levels of NCAM and L1 are associated with patients suffering from neurodegenerative diseases and dementia. Applicant found that the higher levels of both NCAM and L1 are associated with dementia based on correlation analyses. Based on a stepwise multiple regression analysis, there is a significant influence of dementia (a pool of data derived from both neurodegenerative diseases and non-neurodegenerative diseases) and neurodegeneration (a pool of data derived from different neurodegenerative diseases) on the concentration of L1 but not on NCAM in the CSF. Levels of PSA-NCAM in the CSF did not differ among the groups.

In Applicant's pooled samples, 76 of the 108 patients included had Alzheimer's disease. That Applicant sees a statistically significant difference in L1 in a pool of patients suffering from dementia as compared to patients not suffering from dementia is thus presumably due to a difference in AD patients alone, as changes in this marker were

not observed in other dementia-related disorders. Similarly, changes in NCAM in the pooled population were presumably due to the changes in patients with AD alone, as changes in this marker were not observed in other diseases. .

Based on the specification, Applicant is enabled for a method of detecting a higher level of L1 or NCAM in the CSF from patients with Alzheimer's disease. However, the claims are directed to a method of diagnosing a dementia-related neurological disorder in a patient with symptoms of dementia-related neurological disorders or suspected of having the dementia-related neurological disorders by measuring a higher level of at least one cell adhesion molecule selecting from L1 and NCAM. Applicant describes

"the dementia-related neurological disorder that is diagnosed or monitored is any disease or condition that affects or is affected by the central or peripheral nervous systems. The neurological disorder can be degenerative or non-degenerative. A degenerative neurological disorder is used to mean degeneration of any of the cells of the central or peripheral nervous system. Cell types of the central and peripheral nervous systems include, but are not limited to..."

on p. 5 of the specification. However, Applicant fails to provide sufficient guidance as to whether all dementia-related neurological disorders could be diagnosed by an increased level of L1 or NCAM because although most dementia related to neurodegenerative diseases, not all neurodegenerative diseases exhibit a higher level of L1 or NCAM. For example, as described in the specification, dementia is associated with neurodegenerative diseases but multiple sclerosis and Parkinson's disease and other neurodegenerative diseases do not show a higher level of NCAM or L1 (see p.17-18 of the specification and p. 432. 1st col. 3rd paragraph, Massaro A.R. Neurol. Sci. 2002. 22: 429-435).

The instant specification fails to provide sufficient guidance as to enable one of skill in the art to diagnose all dementia-related neurological disorders by detecting an increased level of L1 or NCAM because not all dementia-related neurological disorders could be detected with a higher level of L1 or NCAM. In addition, Applicant is enabled for detecting a higher level of L1 or NCAM in the CSF derived from patients with Alzheimer's diseases, vascular dementia or dementia of mixed type by ELISA using anti-L1 or anti-NCAM antibodies. However, the claims are not limited to detecting the sample derived from CSF. Applicant fails to provide sufficient guidance as to whether all types of samples derived from a patient could be used in the claimed method since the level of L1 or NCAM in the CSF does not necessarily shows a higher level of L1 or NCAM in all biological samples. It has been shown that the protein contents of the CSF could be different from other biological samples. For example the level of beta-trace protein in CSF is much higher than that in serum (p. 882, abstract, Tumani et al. Ann Neurol. 1998. 44: 882-9). Since the level of L1 or NCAM in the CSF does not correlate with the levels of L1 or NCAM in other types of biological samples, it is unpredictable whether detection of a higher level of L1 or NCAM in the CSF could be reproduced in other types of biological samples. Applicant fails to provide sufficient guidance as to enable one of skill in the art to practice the full scope of the claimed subject matter because one can not follow the guidance presented therein and practice the claimed method without first making a substantial inventive contribution. Therefore, in view of the necessity of experimentation, the limited working examples, the unpredictability of the art, and the lack of sufficient guidance in the specification, one of skill in the art

would be required to perform undue experimentation in order to practice the claimed invention as it pertains to a method of diagnosing a dementia-related neurological disorder in a patient with symptoms of dementia-related neurological disorders or suspected of having the dementia-related neurological disorders.

***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 4, 10, 13 are rejected under 35 U.S.C. 102(b) as being anticipated by Massaro AR. (Mult. Scler. 1998. 4: 228-31).

Massaro teaches a method of detecting increased levels of NCAM in the CSF from patients with acute multiple sclerosis as in claims 1, 4, 10, 13 (see p. 228, abstract; p. 229, materials and methods). Multiple sclerosis is also associated with dementia as evidenced by Rao (see p. 250, abstract, Brain Cogn. 1996. 31: 250-68). Thus, claims 1, 4, 10, 13 are rejected anticipated by Massaro AR.

Claims 1, 4, 5, 7, 10, 13, 14, 16 are rejected under 35 U.S.C. 102(b) as being anticipated by Mikkonen et al. (Eur. J. Neurosci. 1999. 11: 1754-1764).

Mikkonen et al. teach a method of detecting a higher level of PSA-NCAM (an isoform of NCAM) in Alzheimer's patients by immunohistochemical staining (see

p.1754, abstract; p. 1756, 2nd col. to p. 1757, 2nd col, 3rd paragraph). The teaching of the reference meets the limitation as in claims 1, 4, 5, 7, 10, 13, 14, 16. Thus, claims 1, 4, 5, 7, 10, 13, 14, 16 are anticipated by Mikkonen et al.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claims 1, 4-10, 13-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Massaro AR. (Mult. Scler. 1998. 4: 228-31) and Mikkonen et al. (Eur. J. Neurosci. 1999. 11: 1754-1764) in view of Lanier et al. (J. Immunol. 1991. 146: 4421-4426 as cited in IDS) and Poltorak et al. (Exp. Neurol. 1995. 131:266-272 as in IDS).

Massaro AR. and Mikkonen et al. teach as set forth above but fail to teach using NCAM 14.2 antibody as anti-NCAM antibody and neuro 4.1 antibody as anti-L1 antibody in the claimed method.

Lanier et al. teach using NCAM 14.2 antibody to detect NCAM (see p. 4421, col. 2nd , 4th paragraph).

Poltorak et al. teach using neuro4.1 antibody and an anti-NCAM antibody to respectively detect the levels of both L1 and NCAM in the CSF derived from patients with Schizophrenia (see p. 267, 1st col. 3rd paragraph). Poltorak et al. also teach that L1 and NCAM function synergistically under certain circumstances and play important roles in CNS development and plasticity (see p. 266, 2nd col., 2nd paragraph; p. 267, 1st col. 2nd paragraph). The teachings of Poltorak et al. provide a motivation and expectation success in using neuro4.1 antibody and an anti-NCAM antibody to detect the levels of both L1 and NCAM adhesion molecules in the CSF.

It would have been obvious to one of ordinary skill in the art at the time the instant invention was made combine the teachings of Massaro AR., Mikkonen et al., Lanier et al. and Poltorak et al. to detect the levels of L1 or NCAM in Alzheimer's disease or multiple sclerosis using NCAM 14.2 antibody and neuro4.1 antibody. The person of ordinary skill in the art would have been motivated to do so because NCAM 14.2 antibody and neuro4.1 antibody can detect NCAM and L1 respectively and the levels of L1 and NCAM are increased in patients with Alzheimer's disease and acute multiple sclerosis. One of ordinary skill in the art would have expected success in detecting increased levels of NCAM and L1 in patients with Alzheimer's disease and acute multiple sclerosis by NCAM14.2 antibody and neuro4.1 antibody since both NCAM 14.2 antibody and neuro4.1 antibody can recognize NCAM and L1 respectively

and patients with Alzheimer's disease or acute multiple sclerosis show a higher level of NCAM.

***Conclusion***

NO CLAIM IS ALLOWED.

Any inquiry of a general nature or relating to the status of this general application should be directed to the Group receptionist whose telephone number is (571) 272-1600.

Papers relating to this application may be submitted to Technology Center 1600, Group 1649 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Should applicant wish to FAX a response, the current FAX number for Group 1600 is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Chang-Yu Wang, Ph.D. whose telephone number is (571) 272-4521. The examiner can normally be reached on Monday-Thursday and every other Friday from 8:30 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Janet Andres, Ph.D., can be reached at (571) 272-0867.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

CYW
January 30, 2007

JANET L. ANDRES
SUPERVISORY PATENT EXAMINER